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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Cho-Chou KUO, et al.

Appln. No.: 09/910,920

Confirmation No.: 2753

Filed: July 24, 2001

Docket No: A8582

Group Art Unit: 1645

Examiner: P. Baskar

For: PHOSPHORYLATED MANNOSE AND CHLAMYDIA INFECTIVITY

SUBMISSION OF APPELLANT'S BRIEF ON APPEAL

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith please find an original and two copies of Appellant's Brief on Appeal. The USPTO is directed and authorized to charge the statutory small entity fee of $165.00 dollars to Deposit Account No. 19-4880. Further, the USPTO is directed and authorized to charge any and all additional required fees, except for the Issue and Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account. A duplicate copy of this paper is attached.

Respectfully submitted,

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Date: October 8, 2003

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PATENT APPLICATION

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APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 1.192, Appellant submits the following:

The following comprises the Appellant's Brief on Appeal from the Office Action dated February 5, 2003, wherein claims 1-4, 6, 8, 17 and 18 were finally rejected. This Appeal Brief is filed in triplicate and is accompanied by a Submission which includes the required appeal fee set forth in 37 C.F.R. § 1.17(c). Appellant's Notice of Appeal was filed on August 5, 2003. A petition for a one month extension of time under 37 C.F.R. § 1.136(a) is submitted herewith. The USPTO is directed and authorized to charge the statutory small entity extension fee of fifty-five ($55.00) dollars to Deposit Account No. 19-4880. Therefore, the present Appeal Brief is timely filed. Further, the USPTO is directed and authorized to charge any and all additional required fees, except for the Issue and Publication Fee, to Deposit Account No. 19-4880.

I. REAL PARTY IN INTEREST

The real party in interest is The University of Washington of Seattle, Washington, the assignee.

II. RELATED APPEALS AND INTERFERENCES

Appellant states that, upon information and belief, Appellant is not aware of any co-pending appeal or interference which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

This is an appeal from the Office Action dated February 5, 2003, wherein claims 1-4, 6, 8, 17 and 18 of the present application were finally rejected. An Advisory Action was mailed August 18, 2003.

The present application was filed on July 24, 2001 with claims 1-16.

In the Election/Restriction dated June 6, 2002, the Examiner required that Applicants elect one of the following groups: Group I, Claims 1-8, drawn to antibody; or Group II, Claims 9-16, drawn to a method of treatment. The Examiner also identified three distinct species, namely mannose-6-phosphate, mannose-6-phosphate receptor, or insulin-like growth factor. In the Response to Restriction Requirement filed on July 3, 2002, Applicants elected with traverse Group I, claims 1-8, as the invention to be prosecuted, and mannose-6-phosphate as the species. Claims 9-16 were withdrawn as directed to a non-elected invention. In the Office Action dated September 10, 2002, the election of species requirement was withdrawn.

In the Amendment filed on December 10, 2002, claim 1 was amended, claims 5 and 7 were canceled without prejudice, and claims 17 and 18 were added as new claims.

In the Amendment filed on June 5, 2003, claim 1 was amended.

No amendments were made to the application after the June 5, 2003 Amendment.

Thus, claims 1-4, 6, 8, 17 and 18 (*see* attached Appendix) are the claims currently on appeal from the final rejection as set forth in the Office Action dated February 5, 2003 and as modified in the Advisory Action dated August 18, 2003.

IV. STATUS OF AMENDMENTS

All of the Amendments listed in section III above have been entered. No Amendments were filed after the final Office Action dated February 5, 2003.

V. SUMMARY OF THE INVENTION

Chlamydiae are obligate intracellular parasites that obtain nutrients and energy from an infected host. Chlamydiae appear to use several ways to enter host cells. Most likely there are multiple entry mechanisms and receptors for Chlamydia, although chlamydial receptors on host cells have remained largely undefined.

The present invention relates to the discovery of novel and unexpected materials and methods for inhibiting the infectivity of Chlamydia (*see* Appellant's specification, page 2, lines 15-17). In particular, the present invention includes the finding by the present inventors that pathogenic Chlamydia organisms have surface structures associated with the major outer membrane protein (MOMP) that bind to the mannose-6-phosphate (Man-6-P) receptor at the

surface of the host cell, facilitating entry of Chlamydia into the host cell. The inventors have also discovered that insulin-like growth factor-2 (IGF-2) enhances the susceptibility of human endothelial cells to infection by Chlamydia pneumoniae (*see* specification, page 3, lines 13-15).

The mannose-6-phosphate (Man-6-P) receptor is a well-characterized multi-functional cell surface molecule, with one binding site for phosphomannosyl residues and another for IGF-2. The two ligands can bind the receptor simultaneously and non-competitively. (*See* specification, page 3, lines 21-25.) Thus, the inventors have discovered that the interaction of the Man-6-P receptor with IGF-2, as well as with Chlamydia organisms, facilitates the entry of Chlamydia into the cell.

The present invention further relates to inhibiting the binding of Chlamydia to mammalian cells, thereby inhibiting infection. The binding by Chlamydia is inhibited by interfering with the interaction between Man-6-P, found on the Chlamydia cell surface, and Man-6-P receptor, found on the surface of the target cell. The inventors discovered that the interaction can be interfered with by molecules that interact with Man-6-P on Chlamydia, Man-6-P receptor on the target cell, or IGF-2 present in the environs of the target cell. (See specification, pages 5-7.)

Examples of molecules that interact with Man-6-P include Man-6-P receptor molecules (specification, page 5, lines 3-4), synthetic molecules that simulate the Man-6-P ligand pocket of Man-6-P receptor (specification, page 6, lines 3-10), and antibodies that specifically bind Man-6-P (specification, page 6, lines 16-19). Examples of molecules that interact with Man-6-P receptor

include modified or unmodified Man-6-P molecules (specification, page 5, lines 10-17), mimetics which simulate the steric conformation of Man-6-P (specification, page 5, lines 18-25), and antibodies that specifically bind Man-6-P receptor (specification, page 6, line 20). Man-6-P receptor antibodies that interact only with the Man-6-P binding site or only with the IGF-2 binding site of the receptor can be designed (specification, pages 6 and 7, lines 20-24 and 1-2 respectively). Examples of molecules that interact with IGF-2 include antibodies that specifically bind IGF-2 (specification, page , lines 5-6).

Thus, the present invention provides a composition comprising:

(a) A Chlamydia infection inhibiting amount of a molecule that interacts with one or both of mannose-6-phosphate and mannose-6-phosphate receptor; and

(b) A pharmaceutically acceptable carrier, diluent, or excipient (Claim 1).

The present invention also provides a composition comprising:

(a) Chlamydia infection inhibiting amount of a molecule that interacts with insulin-like growth factor; and

(b) a pharmaceutically acceptable carrier, diluent, or excipient (Claim 17).

VI. ISSUES

1. Whether claims 1 and 8 are unpatentable under 35 U.S.C. § 102(b) over *Kuo et al.* (J. Clin. Invest., Vol. 98(12), pp. 2813-18) (hereinafter "Kuo").

2. Whether claims 1-4, 6 and 8 are unpatentable under 35 U.S.C. § 102(b) over *Ooij et al.* (Infect. Immun., Vol. 65(2), pp. 758-66) (hereinafter "Ooij").

3. Whether claims 17 and 18 are unpatentable under 35 U.S.C. § 102(b) over *Ooij* (supra).

4. Whether claims 17 and 18 are unpatentable under 35 U.S.C. § 102(b) over *Peterson et al.* (Infect. Immun., Vol 66(8), pp. 3848-55) (hereinafter "Peterson").

VII. GROUPING OF CLAIMS

It is noted that rejected claims 2-4, 6, and 8 stand or fall together with claim 1, as their independent base claim. Further, claim 18 stands or falls together with claim 17, as its independent base claim.

However, claims 1 and 17 do not stand or fall together, but recite separately patentable features. Claim 1 is drawn to a composition comprising a Chlamydia infection inhibiting amount of a molecule that interacts with one or both of mannose-6-phosphate and mannose-6-phosphate receptor. Claim 17 is drawn to a composition comprising a Chlamydia infection inhibiting amount of a molecule that interacts with insulin-like growth factor.

The recitation in claim 1 of a molecule that inhibits Chlamydia infection by interacting with one or both of Man-6-P and Man-6-P receptor does not teach or suggest the recitation in claim 17 of a molecule that inhibits Chlamydial infection by interacting with IGF. Conversely, a molecule that inhibits Chlamydia infection by interacting with IGF does not teach or suggest a molecule that inhibits Chlamydial infection by interacting with one or both of Man-6-P and Man-6-P receptor. A molecule that interacts with one or both of Man-6-P and Man-6-P receptor inhibits infectivity by directly interfering with the binding of Chlamydia to the host cell. On the

other hand, a molecule that interacts with IGF-2 indirectly inhibits infectivity by ameliorating the enhancing effect of IGF-2.

VIII. ARGUMENTS

1. Claims 1 and 8 are patentable under 35 U.S.C. § 102(b) over *Kuo et al.* (J. Clin. Invest., Vol. 98(12), pp. 2813-18).

Kuo does not teach or suggest a "composition comprising a Chlamydia infection inhibiting amount of a molecule that interacts with one or both of mannose-6-phosphate and mannose-6-phosphate receptor" (claim 1) or "the composition of claim 1, wherein said molecule comprises mannose-6-phosphate" (claim 8).

The Kuo article discloses unphosphorylated high-mannose oligosaccharides of *Chlamydia trachomatis* that inhibit Chlamydia infectivity. The major outer membrane protein (MOMP) of Chlamydia is glycosylated with N-linked oligosaccharides (Kuo, page 2813, second column, bottom of first full paragraph). Kuo demonstrates that the carbohydrate moieties of *Chlamydia trachomatis* are predominantly unphosphorylated high-mannose type oligosaccharides (Id.). Furthermore, Kuo teaches that the unphosphorylated oligosaccharides inhibit attachment and infectivity of chlamydial organisms to HeLa cells (Id.). These findings indicate that high-mannose type oligosaccharide is one mediator of attachment and infectivity of Chlamydia to HeLa cells (Kuo, page 2818, first column, top of first full paragraph). Kuo concludes that while the host cell molecule that recognizes the high-mannose oligosaccharides is not yet identified, it may be an analog of the mannose-receptor proteins which are widely

distributed on mammalian cells and have been well characterized (Kuo, page 2818, first column, bottom of second full paragraph).

The mannose receptor is separate and distinct from the Man-6-P receptor, both structurally and functionally. One of ordinary skill in the art knows that phosphorylation, e.g. the addition of a phosphate group, fundamentally changes the nature of the modified molecule. Thus, the mannose receptor interacts with unphosphorylated mannosyl residues and does not bind Man-6-P. Conversely, the Man-6-P receptor interacts with Man-6-P but does not bind unphosphorylated mannose. It follows that the Kuo reference does not teach or even suggest phosphorylated molecules or compositions that interact with Man-6-P or Man-6-P receptor.

The examiner states that Kuo discloses an infection inhibiting composition comprising a high-mannose type oligosaccharide, associated with the major outer membrane protein (MOMP) of Chlamydia, that binds to the Man-6-P receptor on HeLa cells. It appears that the Examiner is improperly assuming first that the high-mannose type oligosaccharides discussed in Kuo are phosphorylated, and second that they must therefor interact with the Man-6-P receptor.

The Examiner may have misinterpreted the sugar structure disclosed in Kuo as Man-6-P. For example, an oligosaccaride structure shown in Table II (Kuo, page 2815) is designated "Manα6." However, in this case the "6" indicates the alpha-linkage of mannose at the 6th carbon position of mannose, and not Man-6-P. Similarly, "oligomannose 6" as listed in Table III (Kuo, page 2817) refers to oligosaccharide containing six mannose residues, not Man-6-P.

As discussed above, the high-mannose oligosaccharides disclosed by Kuo presumably inhibit Chlamydia infectivity by interacting with an unknown mannose-binding protein on the host surface. However, the disclosed oligosaccharides are not Man-6-P. Furthermore, the disclosed oligosaccharides do not interact with Man-6-P or with Man-6-P receptor.

Therefor, Kuo does not teach or suggest a "molecule that interacts with one or both of mannose-6-phosphate or mannose-6-phosphate receptor" as required by claims 1 and 8. Accordingly, Kuo does not teach or suggest the composition of claims 1 and 8. Thus, for at least the reasons set forth above, claims 1 and 8 are patentable over Kuo.

2. Claims 1-4, 6 and 8 are patentable under 35 U.S.C. § 102(b) over *Ooij et al.* (Infect. Immun., 1997, Vol. 65(2), pp. 758-766).

Ooij does not teach or suggest "a composition comprising a Chlamydia infection inhibiting amount of a molecule that interacts with one or both of mannose-6-phosphate and mannose-6-phosphate receptor" (claim 1; see also claims 2-4, which recite that the molecule that "interacts with mannose-6-phosphate or mannose-6-phosphate receptor is an antibody").

Ooij relates to the study of the Chlamydia vacuole, the membrane-bound compartment in the host cell in which the parasite replicates (Ooij, page 758, column 1, first paragraph). Ooij discloses that a monoclonal antibody, specific for the Man-6-P receptor, can be used to label the receptor in cells infected with Chlamydia, thus demonstrating that the Man-6-P receptor is localized in or near the Chlamydial vacuole (Ooij, page 758, abstract).

Cells take up macromolecules from the external medium by a process called endocytosis, in which the endocytosed molecules are initially delivered into small, membrane-bound

intracellular compartments called early endosomes. From early endosomes, some of the ingested molecules are selectively retrieved and recycled to the plasma membrane, while others pass on into late endosomes. Chlamydia, like many other pathogenic bacteria, are internalized through an endocytic pathway and replicate within membrane-bound vacuoles in the host cell.

The involvement of Man-6-P receptor in endocytosis is very well known in the art. Because the Man-6-P receptor has been shown to localize to late endosomes, the receptor is often used as a marker of this compartment. In order to investigate if the Chlamydial vacuole interacts with the late endosomal part of the endocytic pathway, Ooij used a Man-6-P receptor antibody as a tool in visualizing the location of Man-6-P receptor in infected HeLa cells. Based on the localization of Man-6-P receptor and other markers of the endocytic pathway in infected cells, Ooij concludes that the vacuole does interact with late endosomal compartments.

The Examiner states that because Ooij shows that the vacuole containing Chlamydia binds to antibodies to Man-6-P receptor, and the vacuole is known to be involved in Chlamydial replication, Ooij anticipates the claimed invention.

Applicants fail to follow this logic. Ooij did not use the Man-6-P receptor antibody to inhibit Chlamydia infectivity. Instead, as described above, Ooij used the antibody for a completely different purpose, namely as a marker to identify late endosomes Furthermore, Ooij does not in any way indicate that the anti-Man-6-P receptor antibody has any effect on Chlamydial attachment or infectivity, or that the Man-6-P receptor itself has any role in

attachment or infectivity. In fact, the concentration of antibody used in detection assays of this sort is much lower than that which would be needed to achieve inhibition of infection.

Thus, although the Man-6-P receptor antibody disclosed in Ooij undoubtedly interacts with the Man-6-P receptor, the reference does not teach or suggest at least "an infection-inhibiting amount" of a molecule that interacts with Man-6-P receptor, as required by claims 1-4, 6, and 8. Accordingly, Ooij does not teach or suggest the composition of claims 1-4, 6, and 8.

3. Claims 17 and 18 are patentable under 35 U.S.C. § 102(b) over *Ooij et al.* (Infect. Immun., 1997, Vol. 65(2), pp. 758-766).

Ooij does not teach or suggest a composition comprising a "Chlamydia inhibiting amount of a molecule that interacts with insulin-like growth factor" (claim 17), or "the composition of claim 17, wherein said molecule is an antibody" (claim 18).

The Examiner maintains that disclosure by Ooij of an antibody that reacts with Man-6-P receptor is disclosure of an antibody that interacts with IGF-2, because IGF-2 binds to the Man-6-P receptor.

First, there is no indication that the antibody disclosed by Ooij interacts with IGF-2. A person skilled in the art would recognize that binding of the anti-Man-6-P receptor monoclonal antibody to the Man-6-P receptor does not imply that the antibody will also interact with a ligand of the receptor, namely IGF-2. In fact, one of ordinary skill in the art would expect that the anti-Man-6-P receptor monoclonal antibody almost certainly does not bind directly to IGF-2, as antibody binding to a target antigen or epitope is known to be highly specific. And although it is

possible that an anti-Man-6-P antibody could impact the ability of the receptor to interact with IGF-2, e.g. by serendipitously binding at the IGF-2 binding site, this indirect effect would not constitute an "interaction" (between the antibody and IGF-2) as the term is used in the claims and defined in the specification (see specification, p. 5, lines 6-11, 18; page 6, lines 10, 16; page 7, lines 8; 19-21). In any event, Ooij does not indicate that the antibody used has any effect whatsoever on the biological activity of Man-6-P receptor, including the receptor's ability to bind IGF-2.

Finally, as discussed above in section VIII(2), Ooij does not teach or suggest any mechanism whatsoever through which an antibody specific for Man-6-P receptor might influence Chlamydia infectivity.

Thus, Ooij does not teach or suggest "a molecule that interacts with insulin-like growth factor" as required by claims 17 and 18. In addition, Ooij does not teach or suggest "a Chlamydia infection inhibiting amount of a molecule," also as required by claims 17 and 18. For at least these reasons, claims 17 and 18 are patentable over Ooij et al.

4. Claims 17 and 18 are patentable under 35 U.S.C. § 102(b) over Peterson et al. (Infect. Immun., Vol 66(8), pp. 3848-3855).

Peterson does not teach or suggest a composition comprising a "Chlamydia infection inhibiting amount of a molecule that interacts with insulin-like growth factor" (claim 17), or "the composition of claim 17, wherein said molecule is an antibody" (claim 18).

The outer membrane composition of Chlamydia is characterized by a Chlamydial lipopolysaccharide (LPS) as well as by the MOMP discussed above in section VIII(1) (Peterson, page 3848, top of column 2). Peterson teaches a Chlamydia infection inhibiting amount of a monoclonal antibody that specifically recognizes and binds to the LPS of Chlamydia Peterson, page 3848, Abstract). Peterson further elucidates the binding characteristics of the inhibiting antibody by demonstrating that a 3-deoxy-D-*manno*-oct-2-ulosonic acid (Kdo) trisaccaride of the LPS is most likely an essential structural component of the site recognized by the antibody (Id.). The inhibiting antibody does not bind to Man-6-P, or to any other MOMP-associated moiety. These results suggest that the LPS, as well as the MOMP, may have a role in the pathogenesis of Chlamydia (Peterson, page 3854, column 1, bottom of last paragraph).

The Examiner states that Peterson discloses an antibody which inhibits Chlamydia and neutralizes infection, thus inherently interacting with Man-6-P and with IGF-2. The Examiner seems to be assuming that any inhibition of infection must necessarily be mediated through Man-6-P receptor.

This is clearly not the case. Chlamydia organisms are believed to make use of many options and strategies in gaining entry into host cells. For example, the current inventors have previously shown that a mannose-binding protein on the surface of host cells is likely to play a role in attachment and infectivity. (*See* Kuo, discussed above in Section VIII(1).) Because the Chlamydia LPS is a separate macromolecule, clearly distinct from the Chlamydia MOMP (Peterson, page 3854, first column, middle of last paragraph), there is absolutely no suggestion

that the mechanism of inhibition disclosed by Peterson is related to the instant invention or in any other way involves IGF-2.

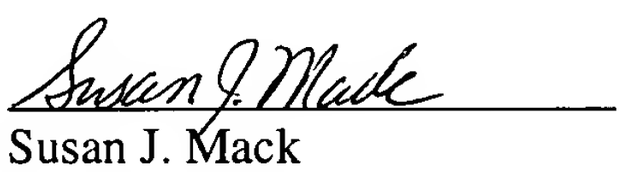
Thus, because Peterson does not teach or suggest at least "a Chlamydia infection inhibiting amount of a molecule that interacts with insulin-like growth factor," as required for claims 17 and 18, claims 17 and 18 are patentable over Peterson.

5. Summary.

In summary, Appellant has invented novel methods of inhibiting Chlamydia infection by disrupting the interaction of target cell Man-6-P receptor with Chlamydial Man-6-P, or the interaction of target cell Man-6-P receptor with IGF-2, which would not have been anticipated from any of the prior art references.

The present Brief on Appeal is being filed in triplicate. Please charge said statutory fee to Deposit Account No. 19-4880. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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Date: October 8, 2003

APPENDIX

CLAIMS 1-4, 6, 8, 17 and 18 ON APPEAL:

1. A composition comprising:

(a) a Chlamydia infection inhibiting amount of a molecule that interacts with one or both of mannose-6-phosphate and mannose-6-phosphate receptor; and

(b) a pharmaceutically acceptable carrier, diluent or excipient.

2. The composition of claim 1, wherein said molecule is an antibody.

3. The composition of claim 2, wherein said antibody specifically binds to mannose-6-phosphate.

4. The composition of claim 2, wherein said antibody specifically binds to a mannose-6-phosphate receptor.

6. The composition of claim 4, wherein said antibody binds to the mannose-6-phosphate binding site.

8. The composition of claim 1, wherein said molecule comprises mannose-6-phosphate.

17. A composition comprising:

(a) Chlamydia infection inhibiting amount of a molecule that interacts with insulin-like growth factor; and

(b) a pharmaceutically acceptable carrier, diluent or excipient.

18. The composition of claim 17, wherein said molecule is an antibody.